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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/792,374	03/03/2004	Ronald Levy	9692-000042	5030

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EXAMINER

YAO, LEI

ART UNIT PAPER NUMBER

1642

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/792,374	Applicant(s) LEVY ET AL.	
	Examiner Lei Yao, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 January 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12,40-56 and 77-92 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) 53,55 and 56 is/are allowed.
- 6) ☐ Claim(s) 1-12,40-52 and 77-92 is/are rejected.
- 7) ☐ Claim(s) 54 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The Amendment filed on 1/4/06 in response to the previous Non-Final Office Action (10/4//05) is acknowledged and has been entered.

Claims 13-39 and 57-76 have been cancelled. Claims 1-5, 8, 10-12, 40-44, and 47-53 have been amended. Claims 77-92 have been added. Claims 1-12, 40-56, and 77-92 are pending and under consideration.

The text of those sections of Title 35, U.S.Code not included in this action can be found in the prior Office Action.

The following office action contains NEW GROUNDS of rejection.

Rejections Withdrawn

1. The rejection of 1-3, 8-9, and 12 under 35 U.S.C. 102(b) as being anticipated by Alizadeh et al., (Nature, Vol 403, page 503-511, February 2000) is withdrawn in view of the amendments to the claims.
2. The rejection of claims 1-3, 8, and 10-12 under 35 U.S.C. 102(b) as being anticipated by Rosenwald et al., (N Engl J Med, vol 346, page 1937-47, June, 2002) or Rocke et al., (US Patent Publication, 2002/0111742, Aug, 15, 2002) is withdrawn in view of the amendments to the claims.
3. The rejection of 1-2, 4-6, 8, 10-11, 40-41, 43-45 and 49 under 35 U.S.C. 102(e) as being anticipated by Gordon et al., (US Patent application Publication, 20030219760, effective filing date, Aug 30, 2002) is withdrawn in view of the amendments to the claims.
4. The rejection of Claims 1 and 4-7 under 35 U.S.C. 103(a) as being unpatentable over Rosenwald et al., (N Engl J Med, vol 346, page 1937-47, June, 2002) in view of Gordon et al., (US Patent application Publication, 20030219760, effective filing date, Aug 30, 2002) and Goldberg et al., (US Patent Publication, 20030060439, effective filing date, 1/11/2001)) is withdrawn in view of the amendments to the claims.
5. The rejection of Claims 40-52 under 35 U.S.C. 103(a) as being unpatentable over Gordon et al., (US Patent application Publication, 20030219760) in view of Alizadeh et al.,

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(Nature, Vol 403, page 503-511) and Goldberg et al., (US Patent Publication, 20030060439) is withdrawn in view of the amendments to the claims.

The following are NEW GROUNDS of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 54 is vague and indefinite because it is not clear whether the claim depend on 52. The value described in the claim seems from claim 53 instead of claim 52. This rejection can be obviated if Applicants amend the claim depending claim 53.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As drawn to new matter

Claims 1-12, 40-52 and 78-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is noted that claims 1-12, 40-52 and 78-92 as newly amended or added claims recite "a first plurality of predictive genes" or "a second plurality of predictive genes", which is not

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supported by instant specification and parental specification. Instant specification as filed, although providing plurality of genes, does not provide sufficient support for the instant claims reciting "a first plurality of genes" or "a second plurality of genes", in the claims.

Claim Rejections-under 35 U.S.C. 103(a)

Claims 1-12, 40-52, and 77-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gordon et al., (US Patent application Publication, 20030219760, effective filing date, Aug 30, 2002) in view of Alizadeh et al., (Nature, Vol 403, page 503-511, February 2000), Rocke et al., (US Patent Publication, 2002/0111742, Aug, 15, 2002), Robetorye et al., (J of Molecular Diagnostics, Vol 4, page 123-136, august 2002), de Vos et al., (Lab Invest, vol 83, page 271-85, Feb, 2003), and Goldberg et al., (US Patent Publication, 20030060439, effective filing date, 1/11/2001).

Gordon et al., teach and suggest a method of diagnosing and predicting the survival of DLBCL patients using the expression profile of plurality of genes (figure 5-9, page 29, para 247, and page 39-40, table 17-20). Gordon et al., teach the correlation between patient survival and matched gene expression and normalization within samples by setting standard and mean (para 189). Gordon et al., teach a method of real time **quantitative RT-PCR** (para 184 and 283). Gordon et al., also teach internal control of GAPDH as a housekeeping gene for the PCR (para 182). Gordon et al., teach **a kit** for a cancer diagnosis comprising measuring the expression of a plurality of genes and analysis of ratio of the expression in cancer cells or cancer samples from patients (page 2, para 20). Gordon et al., also teach a plurality of primers to hybridize to plurality of genes in tumor samples.

Gordon et al., do not teach reference cell line Raji, overall survival after treatment with anthracycline-based chemotherapy, performing univariate Cox hazards analysis, first plurality of gene to normalized to second plurality of gene in DLBCL patient, and housekeeping gene PGK1.

Alizadeh et al., teach the levels of expressing **LMO2, BCL-6, BCL-2** from the samples of DLBCL patients normalized to the control expression comprising **Raji** cell (page 508-509 and fig

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4, and page 510, column 2, para 2). Alizadeh et al., also teach that method predicts the correlation of patient survival with gene expression in the classification groups comprises overall survival after **treatment with anthracycline**-based chemotherapy (page 509, column 2, fig 5 and page 510, line 15-19).

Rocke et al., teach a method of classifying a patient having a DLBCL, comprising measuring expression of a plurality of genes in tumor samples from patient having DLBCL and correlating the gene expression in the classification group (page 1, para 6). Rocke et al., also teach that prediction of patient survival in the classification is determined using the **Cox proportional hazards model** and univariate analysis of the groups (page 13, para 112).

Robetorye et al., or de Vos et al., teach a **plurality of primers** for quantitative RT-PCR to determine or confirm the gene expression pattern in a patient having DLBCL and Robetorye et al., also teach housekeeping gene GAPDH used for control in RT-PCR.

Goldberg et al., teach expression of mRNA, **PGK1**, as internal control of a housekeeping gene (para 46).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method to classify a patient having DLBCL, stratify the classification groups, correlate the expression of the gene to a reference expression, and determine a survival probability by measuring the expression values of plurality genes by real time PCR. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make a kit with all the necessary components comprising plurality of primers for amplifying a plurality of genes in a sample from a patient having DLBCL.

One of ordinary skill in the art would have been motivated with a reasonable expectation of success to apply the teachings of Alizadeh et al., to the teaching of Gordon et al., to use the method of classifying a patient having DLBCL by measuring expression values of the plurality of genes using real time RT-PCR. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to correlate and normalize the expression of the genes to the reference expression and classify the patient having DLBCL because Gordon et al., have shown a method of predicting the survival of DLBCL patients using the expression profile of plurality of

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genes and correlate normalized value to the reference expression and Alizadeh et al., have shown the levels of expressing LMO2, BCL-6, BCL-2 from the samples of DLBCL patients after treatment with anthracycline-based chemotherapy patients and normalizing the expression to the control expression in the cells comprising Raji cell.

One of ordinary skill in the art would have been motivated with a reasonable expectation of success to apply the teachings of Rocke et al., to the teaching of Gordon et al., to use the method of classifying a patient having DLBCL by measuring expression values of the plurality of genes using real time RT-PCR and prediction of patient survival in the classification by the Cox proportional hazards model because Gordon et al., have shown method of predicting the survival of DLBCL patients using the expression profile of plurality of genes and correlation of the value to normalize to reference expression and Rocke et al., have shown a method of classifying a patient having a DLBCL and prediction of patient survival in the classification by the Cox proportional hazards model and univariate analysis of the groups.

One of ordinary skill in the art would have been motivated with a reasonable expectation of success to apply the teachings of Robetorye et al., or de Vos et al., and Goldberg to the teaching of Gordon et al., to use the method of classifying a patient having DLBCL by measuring expression values of the plurality of genes using real time RT-PCR and correlating the normalized expression to the reference expression to classify the patient having DLBCL because, Gordon et al., have shown a method of real time quantitative RT-PCR and correlation and normalization of the expression of the gene and Robetorye et al., or de Vos et al., have shown a plurality of primers for RT-PCR to determine the expression of the genes and Goldberg et al., have shown the expression of mRNA, PGK1, as internal control of a housekeeping gene.

Conclusion

Claims 53 and 55-56 are allowable. The claims 54 may be placed in condition for allowance by resolution of the 112 second paragraph issues by changing the dependence.

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-4.30pm Monday to Friday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY



SHEELA HUFF
PRIMARY EXAMINER